Remarks

Amendments to the Claims

Claim 12 was amended to define the enzymes as in claim 1. Claim 55 was amended to delete a duplicate term.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 12, and 13 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse this rejection. To the extent the rejection confuses written description with enablement, this rejection is also traversed.

Legal Standard

The Court of Appeals for the Federal Circuit (the Federal Circuit) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, e.g.*, *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *See also In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970); *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 U.S.P.Q. 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In addition, as affirmed by the Federal Circuit in *Spectra-*

Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well-known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 U.S.P.Q.2d 1400, 1402, 1404 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986) and are set forth in *In re Wands*. They are: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims. The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." (M.P.E.P. § 2164.01 (a)). Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to these factors. (*Id.*)

In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be

unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982).

There is no requirement for examples. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Further, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The first paragraph of Section 112 provides that the "specification shall contain a written description of the invention..." 35 U.S.C. § 112 (2005). "The description requirement's purposes are to assure that the applicant was in full possession of the claimed subject matter on the application filing date and to allow other inventors to develop and obtain patent protection for later improvements and subservient inventions that build on applicant's teachings." 3-7 Chisum on Patents § 7.04 (2005), citing *Fields v. Conover*, 443 F.2d 1386, 170 U.S.P.Q. 276 (CCPA 1971).

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.*, citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 311, 48 USPQ2d at 1646. As noted in a recent decision by the Board of Appeals and Interferences, the written description requirement does not require a description of the complete structure of every species within a chemical genus. (*see Utter v. Hiraga*, 845 F.2d 993, 998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating "A specification may, within the meaning of 35 U.S.C. § 112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.").

A specification may describe an actual reduction to practice by showing that the inventor constructed *an embodiment* or performed *a process* that met all the limitations of the claim and determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d

1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998) (emphasis added). Although reduction to practice often provides the best evidence that an invention is complete, actual reduction to practice is not required by the written description requirement. An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In *Falkner*, the Federal Circuit recently addressed the issue of written description in an appeal from an interference. *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006). The issue was whether the applicant's priority applications adequately described and enabled a poxvirus-based vaccine. The Federal Circuit reiterated that "[t]he 'written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves to demonstrate that the patentee was in possession of the invention that is claimed." *Falkner* at 1366. The Federal Circuit also clarified that with regard to the written description requirement: (1) examples are not necessary to support the adequacy of the a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. *Falkner* at 1366.

With respect to original claims, the M.P.E.P. states that "there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." M.P.E.P. § 2163(I) (A), *citing In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

Claims 1, 2, 12, and 13 are enabled and comply with written description

Analysis

The Examiner alleges that claims 1, 2, 12, and 13 are not enabled because the specification does not reasonably provide enablement for a linker that is cleaved when the conjugate is exposed to a digestive enzyme chosen from serine proteases and matrix metalloproteinases. Further, the Examiner alleges that claims 1, 2, 12, and 13 are considered reach through claims because the claims read on oligopeptide sequences cleavable by serine proteases and matrix metalloproteinases yet to be discovered or identified.

The Examiner is not applying the appropriate legal standard. As detailed above, the test for enablement is whether one of ordinary skill in the art could make and use the claimed compositions and methods without *undue* experimentation. Whether or not experimentation is undue is a conclusion based on weighing *many* factors, not just a *single* factor, as presented by the Examiner. There is no requirement that all embodiments within a genus be enabled to meet the standard for enablement.

A proper analysis of the *Wands* factors shows that the claimed compositions and methods are enabled. As discussed in detail below, based on the amount of guidance provided in the

specification, the quantity of experimentation necessary, the presence of working examples, and the breadth of the claims, one of ordinary skill in the art would be able to make and use the claimed compositions without undue experimentation.

The breadth of the claims

The claims are restricted to digestive enzymes expressed in the extracellular space of the tissue, which is either a serine protease or a matrix metalloproteinase.

These enzymes are well known. Indeed, a Google search for "serine protease expressed in extracellular" produced many, many examples publications regarding a wide variety of such enzymes and publicly available sources.

The was also true when the search referred to matrix metalloproteinases.

This does not represent a long list of unknown scope but a set of well defined, well understood class of enzymes.

To the extent that the examiner is making a written description rejection, one should note that these enzymes are all well characterized. As the examiner is aware, there is no requirement to provide detailed information on materials which are publicly known and available to the public.

The state of the prior art

In the Office Action mailed March 21, 2007, the Examiner alleged that the state of the art of drug conjugates comprising peptide linkers is high; while the state of the art for using peptide linkers cleavable by digestive enzymes is very low or does not exist (Office Action, page 5).

The Examiner asserts that this is verified by applicants' own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences".

The Examiner has considered only part of the definition of the term "digestive enzyme" provided in the specification. "Digestive enzyme", as defined in the specification, is an enzyme that cleaves polymers. Preferably the cleaved polymers are oligopeptides or oligosaccharides. The claims are restricted to serine proteases and metrix metalloproteinases. These exhibit substrate specificity by definition.

The amount of direction or guidance presented in the application and the quantity of experimentation necessary

Patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner alleges that the specification as filed "does not speak on or show any working examples or studies performed on other cleavable peptide sequences". This conclusion is incorrect.

First, the enzymes within the claimed scope are known and well characterized. Their substrates are also known. One skilled in the art has no difficulty in determining what sequences are cleaved by any of a variety of different enzymes that could cleave the target linker. Moreover, the specification provides numerous details of how to make and use the claimed

subject matter. The specification discloses that a variety of methods known in the art can be used to determine the cleavage motif of a target enzyme when it is not yet known and cites several references describing these methods. Such methods include substrate phase display libraries (Matthew and Wells, *Science*, 260:1113 (1993)); position scanning peptide libraries (Rano *et al.*, *Chem. Biol.*, 4:149 (1996)); and mixture-based peptide libraries (Turk *et al.*, *Nature Biotechnology*, 19:661 (2001)) (page 17, lines 1-17).

The specification discloses that phage display method has been used to determine peptide substrates for a number of proteases, for example, plasmin (Hervio *et al.*, *Chem. Biol.*, 7:443 (2000)); tissue-type plasminogen activator (Ding *et al.*, *Proc. Natl. Acad. Sci. USA*, 92:7627 (1995) and Ke *et al.*, *J. Biol. Chem.*,272:16603 (1997)); prostate-specific antigen (Coombs *et al.*, *Chem. Biol.* 5:475 (1998)); and membrane type-1 matrix metalloproteinases (Ohkubo *et al.*, *Biochem. Biophys. Res. Commun.*, 266:308 (1999)) (page 17, line 18 to page 18, line 2). These references disclose several oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases. Appendix A lists the cleavage motifs for a range of secreted or membrane bound proteases that are overexpressed in certain tumor tissues.

The specification discloses screening techniques which identify sequences which are labile to the target enzyme but resistant to serum proteins (page 18, lines 16 and 17). The specification discloses methods for making the conjugates as well as assays for evaluating whether a particular linker is suitable for use in a conjugate (*see* the Examples). For example,

sets of polymer-linker-drug conjugates or polymer-linker-dye conjugates may be synthesized for kinetic analysis to determine the kinetics of enzyme cleavage (page 19, lines 6-16). The oligopeptides may be synthesized using **conventional solid-phase techniques** and the conjugates may be synthesized using **traditional techniques of peptide coupling** and dextran modification.

In summary, one skilled in the art, once he is told **how and why** he should incorporate a linker which is cleaved by the enzymes defined by the claims, has no difficulty in obtaining a suitable substrate to incorporate into the linker.

The presence of working examples

Although it is not required under 35 U.S.C. §112, first paragraph, the specification provides working examples of the claimed compositions and methods. The Examiner alleges that the Examples do not provide guidance on the use of other peptide linkers and the enzymes which cleave those linkers. This conclusion is incorrect. As discussed above, Appendix A and the references cited in the specification describe peptide substrates for a number of proteases. Examples 1, 5, 6, 7, and 8 describe the synthesis of dextran-oligopeptide-drug conjugates containing doxorubicin or methotrexate. The oligopeptides were synthesized using **conventional solid-phase techniques** and the conjugates may be synthesized using **traditional techniques of peptide coupling** and dextran modification. Examples 2 and 9 describe the peptidyl release or doxorubicin and methotrexate in the presence of MMP-2. Examples 3 and 10 describe *in vitro* cytotoxicity studies of dextran-oligopeptide-drug conjugates containing

doxorubicin and methotrexate. Examples 4 and 11 describe serum stability studies of dextran-oligopeptide-drug conjugates containing doxorubicin and methotrexate.

The quantity of experimentation needed

In the Office Action dated March 21, 2007, the Examiner alleged that the specification fails to provide any support for the use of peptide linkers other than the four oligopeptide sequences cleavable by MMP-2 (Office Action, page 6). Further, the Examiner alleges that the applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation (Office Action, page 6). The Examiner's conclusions are incorrect.

As discussed above, the specification cites several references that disclose oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases. Appendix A lists the cleavage motifs for a range of secreted or membrane bound proteases that are overexpressed in certain tumor tissues. The specification discloses that the peptides can be synthesized using conventional solid-phase techniques (*see* the Examples). The conjugates are synthesized using traditional techniques of peptide coupling and dextran modification. Finally, the specification discloses assays for evaluating whether a particular linker is suitable for use in a conjugate (*see* the Examples). For example, sets of polymer-linker-drug conjugates or polymer-linker-dye conjugates may be synthesized for kinetic analysis to determine the kinetics of enzyme cleavage (page 19, lines 6-16).

Conclusion

Applying the *Wands* factors, one sees that the specification provides a high level of detail for the claimed conjugates and methods of making and characterizing thereof. The level of skill in the art is high, and one of ordinary skill in the art is aware of a variety of oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases. The specification also provides working examples containing oligopeptides which are cleavable by MMP-2. Finally, the claims are not overly broad. Therefore, one of ordinary skill in the art could make and use the claimed compositions without undue experimentation. Therefore, claims 1, 2, 12, and 13 are enabled and comply with the written description requirement.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1, 4, 5, 12, and 13 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Legal Standard

A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as any special meaning assigned to a term is clearly set forth in the specification. See MPEP § 2111.01. Applicant may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As

noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

Analysis

The Examiner alleges that the terms "drug molecule" or "small molecule drug" or a "biomolecular drug" in claims 1, 4, 5, and 12-13 are extremely broad and thus one of ordinary skill in the art would not be apprised of the scope of the claimed subject matter as to the types of drug which could be used. The Examiner's conclusion is incorrect.

A "small molecule drug" is a naturally-occurring or synthetic molecule that has a relatively low molecular weight and is not a protein, nucleic acid, or a carbohydrate (page 13, lines 14-16). Typically, although not necessarily, small molecule drugs are monomeric and have a molecular weight of less than 1500 g/mol (page 13, lines 16-18). Examples of classes of small molecule drugs are listed on page 14, lines 3-16. A "biomolecular drug" is a naturally-occurring or synthetic molecule that has a relatively high molecular weight and is a protein, nucleic acid, or carbohydrate. Typically, though not necessarily, biomolecular drugs have a molecular weight greater than about 1500 g/mol (page 15, lines 3 and 4). Examples of classes of biomolecular drugs are listed on page 15, lines 5-9. Applicants are their own lexicographers. Applicants have defined the terms in question in the specification. One of ordinary skill in the art would understand the meaning of the terms "small molecule drug" and "biomolecular drug" when read in light of the specification. Thus, claims 1, 5, 12, and 13 are definite.

The Examiner also alleged that the phrase "size of the polymeric carrier is larger than the renal excretion limit" in claim 4 is indefinite. Specifically, the Examiner alleges that this phrase is not defined in the claim and that the specification does not provide a standard for ascertaining the requisite degree. The Examiner's conclusion is incorrect. The specification discloses that, in certain embodiments, the polymeric carrier allows conjugates and hence drugs to circulate longer in plasma by decreasing renal excretion and liver clearance (page 9, lines 6-9). Hashida and Takakura relate the physiological features of the liver and kidneys to the clearance data obtained with macromolecules (page 9, lines 9-12). For example, macromolecules with size above 6 nm (MW ~ 50,000 Daltons) exhibit marked inhibition on renal clearance. Applicants are their own lexicographers. Applicants have defined the phrase in question in the specification. One of ordinary skill in the art would understand the meaning of the phrase "size of the polymeric carrier is larger than the renal excretion limit" when read in light of the specification. Thus, claim 4 is definite.

Rejection Under 35 U.S.C. § 102

Claims 1-6, 9-13, 17-22, 29, 33, 39, 43, 47-52, and 54-56 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/68145 to Copeland *et al.* ("Copeland"). Applicants respectfully traverse this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech*

Inc. v Monoclonal Antibodies Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found v. Genentech Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 U.S.P .Q.2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. [...] There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

Id.

For a prior art reference to anticipate a claim, it must enable a person of ordinary skill in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. [...] [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not

suffice as prior art if it was not enabling." *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986).

Analysis

Copeland does not disclose or suggest compositions containing a polymeric carrier as required by the independent claims

Copeland describes compositions containing antineoplastic agents conjugated to enzyme cleavable peptides containing the amino acid recognition sequence of a membrane-bound and/or cell secreted peptidase (abstract). The peptide is capped with a capping group (page 5, line 31). Suitable capping groups are discussed beginning at page 42, line 26. Copeland discloses that polyethylene glycols can be used as amino-capping groups (page 43, lines 17-22). Copeland defines "polyethylene glycol", or "PEG" or "Peg" as an amino capping group having the formula shown below:

$$H_3COCH_2CH_2OCH_2CH_2OCH_2C(=O)-$$

This is not a polymer. This molecule contains only two monomer units. Copeland does not disclose or suggest a composition containing a polymeric carrier as required by the claims. According, claims 1, 5, 6, 9-13, 17-22, 29, 33, 39, 43, 47-52, and 54-56 are novel over Copeland.

Copeland does not disclose or suggest polymeric carriers having a size larger than the renal excretion limit as required in claim 4

Claim 4 depends from claim 1 and specifies that the size of the polymeric carrier is larger than the renal excretion limit. The specification discloses that macromolecules with sizes above,

for example, 6 nm (MW ~ 50,000 Daltons) exhibit marked inhibition on renal clearance. Copeland does not disclose an amino-capping group having sizes above 6 nm. Accordingly, claim 4 is novel over Copeland.

Copeland does not disclose or suggest the amino acid sequences in claims 15 and 16

In the office action mailed March 21, 2007, the Examiner acknowledged the novelty of claims 15 and 16 over Copeland (Office Action, page 8). However, the Examiner rejected claims 18-20 and 22 as lacking novelty over Copeland. Claims 18-20 and 22 depend from either claims 14 or 15. Accordingly, claims 18-20 and 22 are novel over Copeland.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 9-14, 17-22, 29, 33, 39, 43, 44, 47-52, and 54-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/56425 to Duncan, in view of Copeland. Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> "The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the priort art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use

hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham* , 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964))).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

Analysis

As discussed above, the United States Supreme Court in *KSR* reaffirmed the *Graham* factors an obviousness analysis. The *Graham* factors are analyzed below:

(a) Determining the scope and contents of the prior art

The scope and contents of the prior art must be made *at the time the invention was made*. The requirement " at the time the invention was made" is to avoid impermissible hindsight. "It is

difficult but necessary that the decision maker forget what he or she has been taught [...] about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983).

Duncan describes a product or kit containing two components, i.e., two pharmaceutical compositions that are arranged or otherwise adapted for sequential administration to a human or animal (page 3, line 36 to page 4, line 2). The first component is an enzyme conjugate, e.g., a composition that contains a pharmaceutically acceptable excipient and an enzyme conjugate (page 4, lines 2-5). The enzyme conjugate may consist of an enzyme covalently bound to a polymeric or other carrier, such that the enzyme conjugate retains its enzyme activity (page 4, lines 5-7). The second component is a prodrug, e.g., a composition that contains a pharmaceutically acceptable excipient and a prodrug (page 4, lines 8-10). Duncan does not disclose or suggest a conjugate containing a polymeric carrier; a drug molecule; and a linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker. Further, Duncan does not disclose or suggest the linkers defined in claims 15 and 16.

Copeland is discussed above. Copeland does not disclose or suggest a composition containing a polymeric carrier as required by the claims. Further, Copeland does not disclose or suggest the linkers defined in claims 15 and 16.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The Claimed Compositions and Methods

The claims define a conjugate for use in targeting a drug to a tissue, wherein a digestive enzyme is overexpressed in the extracellular space of the tissue. As discussed in the specification, such conjugates allow the conjugate to circulate longer in plasma by decreasing renal excretion and liver clearance.

Independent claim 1 and its dependent claims, define conjugates for use in targeting a drug to a tissue, wherein a digestive enzyme is overexpressed in the extracellular space of the tissue comprising:

a polymeric carrier;

a drug molecule; and

a linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker.

Claim 12 defines a method of preparing a conjugate for use in targeting a drug to a tissue, wherein the tissue overexpresses a digestive enzyme, the method comprising:

providing a polymer carrier;

providing a drug molecule;

providing a linker that includes at least a first end and a second end, wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to the digestive enzyme; wherein the digestive enzyme us selected from the group consisting of serine proteases and matrix metalloproteinases;

associating the polymer carrier with the first end of the linker; and

associating the drug molecule with the second end of the linker.

Claim 13 and its dependent claims define a method of targeting a drug to a tissue in a patient, wherein a digestive enzyme is overexpressed in the extracellular space of the tissue, the method comprising the steps of:

providing a patient;

providing a pharmaceutical composition that comprises a pharmaceutically acceptable excipient and an effective amount of a conjugate; and

administering the pharmaceutical composition to the patient; wherein the conjugate comprises:

a polymeric carrier;

a drug molecule; and

a linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker; wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to the digestive enzyme; and wherein the digestive enzyme is selected from the group consisting of serine proteases and matrix metalloproteinases.

The claimed compositions and methods do not require sequential administration of two compositions as required by Duncan. The claimed compositions are cleaved by enzymes overexpressed **at the desired target site**. In contrast, Duncan requires administration of an enzyme conjugate to achieve overexpression.

One of ordinary skill in the art would not be motivated to combine Duncan and Copeland to arrive at the claimed conjugates

As discussed above, Duncan discloses a product or kit containing two components, i.e., two pharmaceutical compositions that are arranged or otherwise adapted for sequential administration to a human or animal (page 3, line 36 to page 4, line 2). The first component is an enzyme conjugate, e.g., a composition that contains a pharmaceutically acceptable excipient and an enzyme conjugate (page 4, lines 2-5). The enzyme conjugate may consist of an enzyme covalently bound to a polymeric or other carrier, such that the enzyme conjugate retains its enzyme activity (page 4, lines 5-7). The second component is a prodrug, e.g., a composition that contains a pharmaceutically acceptable excipient and a prodrug (page 4, lines 8-10). Duncan does not disclose or suggest a conjugate containing a polymeric carrier; a drug molecule; and a

linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker. Duncan requires administration of an enzyme conjugate to achieve overexpression. In contrast, the claimed compositions are cleaved by enzymes overexpressed **at the desired target site**.

Copeland discloses compositions containing antineoplastic agents conjugated to enzyme cleavable peptides containing the amino acid recognition sequence of a membrane-bound and/or cell secreted peptidase (abstract). Copeland does not disclose or suggest a composition containing a polymeric carrier as required by the claims. One of ordinary skill in the art would not be motivated to combine the two-component compositions of Duncan with the non-polymeric compositions of Copeland to arrive at the claimed conjugates. Accordingly, claims 1-6, 9-14, 17-22, 29, 33, 39, 43, 44, 47-52, and 54-56.

Double Patenting Rejection

Claims 1-13 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 and 16 of Application Serial No. 60/779,401. Applicants respectfully traverse this rejection.

The Examiner has made a double patenting rejection over a lapsed U.S. provisional application. This is an improper rejection.

The doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity beyond the term of a patent. The public policy behind this doctrine is that: the public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to

use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill in the art and prior art other than the invention claimed in the issued patent.

In re Zickendraht, 319 F.2d 225, 232, 138 USPQ 22, 27 (CCPA 1963) (Rich, J., concurring). Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982). A patent cannot issue on a provisional application since such applications are not examined. Thus, the Examiner must withdraw the double patenting rejection.

Allowance of claims 1-6, 9-23, 29, 33, 39, and 43-56, as amended, is respectfully solicited.

Respectfully submitted,

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